

approaching happiness

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We all know what happiness is. At least we know what it feels like to be happy. But the moment you begin to define it, things become complex. And trying to measure a feeling as ungraspable as happiness seems as far-fetched as weighing a poem. Yet understanding what sculpts high spirits is essential; as essential as understanding feelings at the other end of the scale – such as depression for instance. Over the years, scientists have demonstrated that there is undoubtedly a genetic component to happiness, as there is to depression. A gene discovered in the 1960s and known to be involved in antisocial behaviour has actually turned out to have its say in human happiness as well. Depending, that is, on how strongly the gene is expressed and an array of sociocultural, physiological and anatomical parameters. The gene is known as MAOA – for monoamine oxidase A – an enzyme that metabolizes neurotransmitters which each have their say in modulating our mood. And since MAOA is located on the X chromosome, it is argued that it influences happiness in women while, surprisingly, it has little incidence on men.



Approaching happiness, by Carol White

Courtesy of the artist

From a historical point of view, happiness was first defined as a condition that depended on events that were exterior to an individual, such as good luck or the prospect of a long-expected journey. As time went by and the notion of happiness began to revolve around something more self-centred, happiness became synonymous with a person's well-being.

Cheerfulness and its making – or indeed its undoing – is currently understood as the intricate result of a sum of situations in which an individual is immersed. Namely: a person's age, gender, education, household income, marital status, employment status, mental disorder, physical health, relationship quality, religiosity, abuse history, recent negative life events and self-esteem. With the belief that happiness is something every human will naturally lean towards if doused in the "right" conditions.

Moods, however, are not solely due to circumstances outside an individual. Over the years it has become obvious that there is a genetic component to our traits of character too; something a mood can be built upon. So scientists turned to the genome to pin down genes that meddle with our humour. Antisocial personality traits are so diffuse and have such harmful effects on society in general that they have been intensively studied. And this is how, back in the 1960s, MAOA was identified as a gene that could have something to do with a person's antisocial behaviour. But these are notions to be handled with great care. Considerations such as these can be – and have been – used in legal procedures to lighten a sentence for instance. Genetic predisposition to antisocial behaviour does seem to exist, i.e. it can trigger off antisocial behaviour depending on a given life event. An example would be

child abuse. However, a person who carries the predisposition and has suffered child abuse does not necessarily develop aggressive behaviour. The difference is subtle but important to grasp.

So how can MAOA be involved in two states of mind that are situated on the opposite ends of the mood scale? First: a brief introduction to the enzyme behind MAOA. MAOA is a flavoenzyme that catalyses the oxidation of three neurotransmitters – dopamine, noradrenaline and serotonin – with the help of its cofactor flavin adenine dinucleotide (FAD). These three neurotransmitters are part of many different pathways amongst which those that tamper with mood regulation. Dopamine, as an illustration, is linked to our reward-motivated behaviour and has its say in depression and mania but also cognitive alertness. Noradrenaline is responsible for vigilant concentration and may well be involved in decision-making. And serotonin seems to play an important part in our feelings of well-being and happiness. To cut a long story short, when MAOA is expressed at low levels, it seems to mark a predisposition to antisocial behaviour. When it is expressed at higher levels, it could predispose us to happiness. And the fact that it is X-linked has made scientists wonder whether women are then more prone to happiness than men. But things have proved to be far more complex: an increased amount of MAOA does not make men happier.

MAOA could be compared to a corkscrew. The main body is made of two globular parts: one holds the cavity into which slips one of the three neurotransmitters (or indeed inhibitor); the

second is the co-factor FAD binding domain. The corkscrew *per se* protrudes from the main body of the enzyme as a helix which is inserted into the mitochondrial membrane thus anchoring the enzyme on the mitochondrion's surface. To date it is not known why the mitochondrion was chosen as a place of mooring but anchoring is necessary for enzyme activity. The active site of MAOA is almost a sealed cavity whose opening is very narrow thus making it difficult for the substrate to squeeze through. However, when MAOA is inserted into the mitochondrial membrane, the whole structure becomes more supple and the substrate is able to slip into the active site.

Monoamine oxidases are important flavoenzymes that, over the years, have been linked to many psychiatric disorders. Happiness is far from a psychiatric disorder but it is a state whose detailed molecular description can help understand disabling mood disorders. MAOA is involved in antisocial behaviour but also in happiness, thus making it an ideal target for drug design. This said, happiness is dependent on many external parameters, and so will the efficiency of an MAOA-targeted drug. And to make things more complicated, studies have shown that the epigenetic methylation of MAOA could have a role in alcoholism and nicotine addiction in women. It is all so very complex and the more you read about happiness, what it means and how to measure it, the less you seem to know. And yet, the laugh of a child or a glint in an old woman's eye is able to express it in a fraction of a second.

Cross-references to UniProt

Amine oxidase (flavin-containing) A, *Homo sapiens* (Human): P21397
Amine oxidase (flavin-containing) A, *Rattus norvegicus* (Rat): P21396

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